

IS THERE A ROLE FOR COMBINATION THERAPY IN MS?

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IFNs and GA are partially effective and are insufficient to completely suppress inflammatory disease activity in a majority of patients with RRMS or SPMS. 35% of treated patients showed less than 90% suppression of new enhancing lesions. As enhancing lesions are associated with increased relapse rates and increased T₂ lesion burden the continuing appearance of new enhancing lesions suggests an inadequate response to treatment.

These facts support the use of combination treatment to enhance efficacy, reduce inflammation and improve control activity in patients with MS. However inflammation in general may not be considered as an enemy that we have to fight as not all products of inflammation are bad.

Most important concern is that combination of therapies with different mechanisms may compete with each other and so combined effect may be less than with either agent alone. An example is the different mechanisms of action that have Glatiramer acetate (GA) and interferon beta (IFNβ-1α and IFNβ-1β). There is the possibility that the action of IFNbeta on reducing T cell migration could prevent the cells generated by GA from entering the CNS.

Additionally combined effects could mean combined new or unexpected toxicities as it happened with the combination treatment with Natalizumab and Interferon Beta-1a for relapsing remitting MS. This treatment led to unexpected surprises with two cases of progressive multifocal leukoencephalopathy.

Combination therapies should be avoided in the absence of data suggesting that a particular combination of agents is more effective than either one alone and must not be given before there are critical data demonstrating that the combination is at least safe.

One cannot assume on the basis of mechanism of action that the addition of an agent to a standard immunomodulatory therapy is safe. The new drug given may have no additional effect or may antagonize the effect of IFNbeta or GA.

There are still no randomized placebo controlled blind studies estimating the efficacy and the safety of combination therapies. Some are currently being evaluated in controlled settings.

Nowadays the use of Natalizumab in MS patients who continue having relapses although they are in treatment with IFNbeta holds back the combination therapies at least for the two years treatment with Natalizumab after stopping the treatment with IFNbeta.